Acute kidney injury: changing lexicography, definitions, and epidemiology

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In recent years, there have been numerous advances in understanding the molecular determinants of functional kidney injury after ischemic and/or toxic exposure. However, translation of successful novel therapies designed to attenuate kidney functional injury from animal models to the clinical sphere has had modest results. This lack of translatability is at least in part due to lack of sufficient standardization in definitions and classification of cases of acute kidney injury (AKI), an incomplete understanding of the natural history of human AKI, and a limited understanding of how kidney injury interacts with other organ system failure in the context of systemic metabolic abnormalities. A concerted effort is now being made by nephrologists and intensivists to arrive at standardized terminology and classification of AKI. There have also been dramatic advances in our understanding of the epidemiology and natural history of AKI, particularly in the hospital and intensive care unit setting. Promising strategies are now being developed which may ultimately lead to improved outcomes for patients at risk for or who have developed AKI, which should be readily testable in the coming decade.

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LEXICOGRAPHY

The lexicography of what is now best termed acute kidney injury (AKI) is richly related to many important historical figures in the history of medicine and the study of kidney diseases.[1] It was William Heberden in his 'Commentaries on the History and Cure of Diseases' who first described the clinical course of AKI (then termed 'ischuria renalis') in 1802. Bowman, Charcot, and William Osler all made important contributions. However, the syndrome was largely overlooked until Bywaters and Beal classically described anuric AKI after crush syndrome during the German bombing of London during WWII. Also during WWII, Andre Cournand (later winner of the 1956 Nobel Prize in Physiology or Medicine) and co-workers were the first to study extensively changes in kidney function associated with circulatory failure or shock in man during an investigation carried out at Bellevue Hospital.

Perhaps, the modern era in the study of AKI truly began in 1951, when Homer W Smith introduced the term acute renal failure in his seminal text 'The Kidney – Structure and Function in Health and Disease.'[2] Smith comprehensively reviewed data from animal models, as well as physiologic, pathologic, and clinical data from human cases of acute renal failure. Still of interest today, Smith provided clinical advice for the treatment of anuria. 'The treatment of anuria should be conservative. If circulatory failure is present, appropriate steps should be taken to correct it. Otherwise, therapy is limited to the balanced maintenance of the patient until the kidneys have a chance to affect recovery…It is now widely recognized that a serious mistake of the past has been the zealous overadministration of fluid on the theory that the anuric patient was 'dehydrated'…It is easy to expand the body fluids to such an extent as to produce dangerous pulmonary edema and perhaps to promote the formation of renal edema.…Although the artificial kidney, peritoneal dialysis, replacement transfusion, and intestinal irrigation are possibly useful in some cases in supporting the patient through a critical period of uremia, the indications for their use are not clearly defined. They cannot in themselves induce diuresis and their value in influencing the course of acute anuria, usually a self-limited disturbance, defies critical evaluation. Because each method involves an inherent physiologic burden, the application of any of them may handicap rather than promote spontaneous recovery. The

most notable aspect of this problem is the remarkable capacity of the renal parenchyma to reconstitute itself after devastating injury.'[2]

Homer Smith's term acute renal failure stood the test of time until the twenty-first century. Recently, a group of international experts (comprised both nephrologists and intensivists) have attempted to develop a broad consensus on new definitions and terminology for acute renal failure. First known as the Acute Dialysis Quality Initiative (ADQI) and later as the AKI Network (AKIN), this group has proposed the term 'acute kidney injury' to redefine the entire spectrum of acute renal dysfunction, encompassing early and mild forms all the way to severe forms requiring renal-replacement therapy. This change in terminology was prompted by several considerations, including:

1. The recognition that even relatively modest changes in serum creatinine are highly associated with adverse outcomes in hospitalized patients, this suggesting that the syndrome should encompass more than outright kidney failure;
2. Recognition that the term 'injury' more accurately conveys the associated pathobiology than the term 'failure'; and
3. Recognition that the English word 'kidney' is more readily understood by the general public than the Latin-derived word 'renal.'

DEFINITIONS OF AKI

The desire to standardize the definition of AKI is prompted by recognition that the published literature contains a strikingly wide spectrum of definitions, making cross-comparison between studies difficult (reviewed by Mehta and Chertow).[3] Indeed, in a recent survey, at least 35 separate definitions of AKI were identified in the literature. To date, all definitions of AKI have relied on either an abrupt increase in serum creatinine (to denote a reduction in glomerular filtration rate) or an abrupt decline in urine output. Recently, tremendous interest has been generated in the development of urinary and blood biomarkers that may be able to detect early AKI before a rise in serum creatinine.[4] However, although several biomarkers hold great promise with respect to the ability to create a new paradigm in the definition of AKI, to date clinical biomarker studies have generally been performed as single center studies and their positive and negative predictive value have not been validated in multiple heterogenous populations. Thus, for the present, definitions and classification of AKI continue to revolve around changes in serum creatinine and urine output.

A key element has been the emergence of data from multiple studies demonstrating that relatively small decreases in kidney function are prognostically important. Over a decade ago, Levy *et al.*[5] demonstrated that at 25% increase in serum creatinine after exposure to radiocontrast material was associated with greatly increased odds of death. In a study using a hospital-wide database, any increase of serum creatinine of greater than 0.3 mg/dl was independently associated with increased costs and mortality risks (Table 1).[6] Similar data have also been obtained in studies of AKI after cardiac surgery and other cardiac conditions.[7] These data have spawned new definitions of AKI dependent on relatively small changes in serum creatinine, thereby increasing the prevalence of AKI.

The RIFLE (Risk, Injury, and Failure with the outcome classes Loss and End-stage kidney disease) criteria combine severity grades based on changes in serum creatinine or urine output with clinical outcome criteria (Figure 1). Early studies suggest that use of RIFLE criteria in the intensive care unit (ICU) setting conveys significant prognostic information in the majority of studies.[8] More recently, the AKI network has suggested a more simplified definition which depends only on a greater than 0.3 mg/dl (>25 mmol/l) rise or a $>50\%$ increase in serum creatinine or the development of oliguria as defined by urine output <0.5 ml/kg/h for greater than 6 h.

Table 1 | Hospital-acquired AKI: mortality and cost associated with selected changes in SCr

Increase in SCr (mg/dl)	Multivariable OR (95% CI)	Area under ROC curve	Increase in total cost
0.3	4.1 (3.1–5.5)	0.84	$4,886
0.5	6.5 (5.0–8.5)	0.86	$7,499
1.0	9.7 (7.1–13.2)	0.84	$13,200
2.0	16.4 (10.3–26)	0.83	$22,023

AKI, acute kidney injury; CI, confidence interval; OR, odds ratio; ROC, receiving operating characteristic; SCr, serum creatinine.

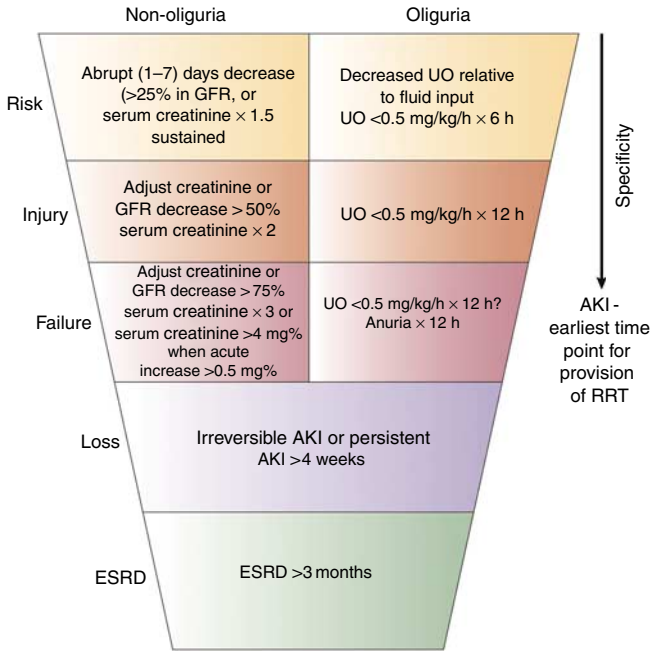

Figure 1 | RIFLE Criteria for Diagnosis of AKI. Adapted with permission from Lameire *et al.*[16]

Whether this definition can provide a common clinical classification for all cases of AKI with adequate prognostic information remains to be prospectively validated.

EPIDEMIOLOGY

Determination of the prevalence of AKI is dependent on the definition employed and is also dependent on methods used for ascertainment of cases. It is possible that all studies of the epidemiology of AKI underestimate the prevalence rate, regardless of the clinical setting, as patients are rarely universally screened for changes in estimated glomerular filtration rate or urine output. The incidence of AKI also varies with the clinical setting and studies have separately addressed community-, hospital-acquired, sepsis-induced, and ICU-associated AKI.

Community-acquired AKI

There have been relatively few systematic studies of the epidemiology of community-acquired AKI and those that have been accomplished report widely varying rates of AKI occurrence, depending on the definition utilized and the community. Overall, annual rates of the incidence of AKI vary from 22 to 620/million population. The definitional dependence of the incidence of community-acquired AKI is illustrated by a British study in which annual incidence rates using the need for renal replacement therapy as a definition was 22/million population vs. 175/million population using the definition of a serum creatinine >5.7 mg/dl ($>500\,\mu$mol/l).[9] A similar study in Scotland reported an annual incidence of 50/million population using the need for renal replacement therapy compared with 102/million population with a serum creatinine >5.7 mg/dl ($\geqslant 500\,\mu$mol/l) and 620/million population using a serum creatinine >3.4 mg/dl ($\geqslant 300\,\mu$mol/l).[10] A community-based study from the Madrid region reported an annual incidence of 209/million population using a complex definition accounting for baseline level of kidney function and the rate of rise in serum creatinine.[11] There has never been a comprehensive community-based study of the incidence of AKI in the US, although community-acquired AKI may account for 1% of hospital admissions.[12] In tropical settings, the etiology of community-acquired AKI may vary, as diarrheal illnesses, infectious diseases, and snakebites are still common causes of AKI. Botanical nephrotoxins and alternative medical therapies also contribute to AKI in these clinical settings. Natural disasters such as earthquakes with resulting crush-syndrome victims contribute to local and regional epidemics of AKI.

Hospital-acquired AKI

A number of recent studies have increased our understanding of the incidence of AKI in hospitalized patients. Two recent studies have used administrative and claims databases to provide a national sample of the incidence of mortality of AKI in the US.[13,14] Both studies were large, with each study evaluating more than 5 000 000 hospital discharges. Although reported prevalence rates and mortalities differed between the two studies, each study documented that the prevalence of AKI in hospitalized patients steadily increased over time, with a concomitant trend towards decreased mortality (Figure 2). In evaluating these studies, it is worth noting that those studies relied on the validity of utilizing the International Classification of Diseases, 9th revision, Clinical Modification Codes (ICD-9-CM) for AKI. The performance characteristics of the ICD-9-CM codes for AKI were compared with serum creatinine-based definitions of AKI in nearly 100 000 discharges from three Boston hospitals.[15] There is a very high specificity (97.7%) for AKI with only modest sensitivity (35.4%). Thus, administrative and claims database-based evaluations of the prevalence of AKI in hospitalized patients possibly severely underestimate morbidity, mortality, and cost associated with AKI. The increase in the prevalence of hospital-acquired AKI over time parallels the increased prevalence of sepsis in hospitalized patients, a major contributor to AKI in this setting.

Several single-center studies have reported that AKI occurs in 5–7% of hospitalized patients.[16] These data suggest that hospital-acquired AKI exceeds the prevalence of a community-acquired AKI 5–10-fold and that the major causes of hospital-acquired AKI are changing. The incidence of post-

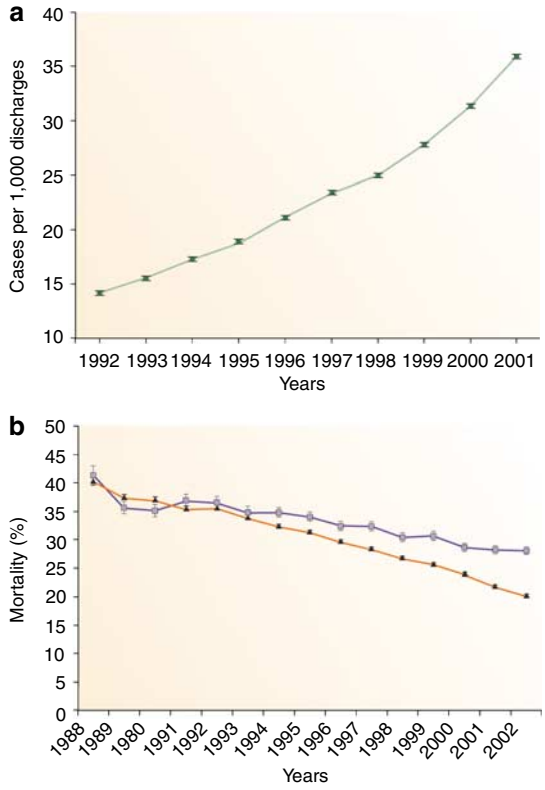

Figure 2 | AKI: changing prevalence and mortality using nationally-represented databases. (**a**) Increasing prevalence of hospital-associated AKI. Adapted with permission from Xue *et al.*[13] (**b**) Dialysis mortality with hospital-associated AKI. (▲) AKI; (□) AKI requiring dialysis. Adapted with permission from Waikar *et al.*[14]

operative AKI is decreasing, whereas newer etiologies, including HIV nephropathy, AKI after solid organ transplantation, and after cardiac resuscitation are increasing. Similarly, although the incidence of AKI because of antibiotic use is declining, cases of hospital-acquired AKI owing to the use of nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme-inhibitors, chemotherapeutic agents, and antiviral agents is increasing. Of interest, the prevalence of acute or chronic kidney injury appears to be increasing globally as the prevalence of chronic kidney disease increases. In the two previously mentioned national samples from administrative and claims data in the US, patients with chronic kidney disease were three times as likely to develop AKI. In a recent study from China, acute or chronic kidney injury accounted for nearly 36% of biopsied AKI cases.[17] Obstetric causes of hospital-acquired AKI, although still prevalent in some environments, such as in India, are also declining.[18]

Sepsis-induced AKI

In the US, sepsis accounts for approximately 750 000 hospital admissions annually, with an overall mortality rate of approximately 30%. Half of these patients require ICU admission. In the US, the incidence of sepsis-related hospital admissions appears to be rising at a rate between 1.5 and 8% per year.[19] and international epidemiologic studies suggest that sepsis now accounts for 17% of all medical ICU admissions. The incidence of AKI is increasing in parallel to the incidence of sepsis.[19] Kidney injury among the elderly as a complication of sepsis is especially common; of the 6% of ICU patients who develop AKI, the median age is 67, with 30% of these patients having pre-existing renal dysfunction. The dominant risk factor for AKI among hospitalized patients is sepsis, occurring in about half of kidney failure in the ICU setting.[20]

A stepwise increase in AKI occurs as patients progress from sepsis to septic shock. Thus, AKI occurred in 19 of patients with sepsis, 23 with severe sepsis, and 51% with septic shock with positive blood cultures.[21] Though recent advances in critical care management have improved overall ICU survival, the same cannot be said for the critically ill with AKI. Even in patients not requiring dialysis, AKI worsens prognosis in critical illness; when dialysis is required, the ICU mortality rises to 45–80%. Although the development of AKI clearly is a marker of disease severity and adverse prognosis, the extent to which the development of AKI actually contributes to other organ system failure is an area of active inquiry. Critically ill patients with pre-existing end-stage renal disease have a better prognosis than when AKI develops during sepsis, suggesting that the outcome is associated with systemic disease in addition to kidney dysfunction itself.[22]

ICU-associated AKI

Development of AKI occurs frequently in the ICU setting.[20] Consistent with the complexity of their disease state, a plethora of studies have indicated that mortality ranges between 23 and 79% in this patient population. Given the excess mortality rates, much effort has been placed on accurately predicting in-hospital mortality in critically ill AKI patients. Such prediction models are important for clinical decision-making, quality improvement, and design of future clinical trials. Studies to date have attempted to either validate generic or disease-specific predictive instruments or have derived new predictive models.[23] However, most studies have been developed from single centers and have examined risk factors at a single point in time. Recently, the Program to Improve Care in Acute Renal Disease, a registry of critically ill patients with AKI across multiple US clinical sites, developed models for prognostic stratification and risk adjustment for mortality after AKI. To extend previously published work, this analysis provided separate predictive models at three time points during the course of AKI (day of AKI diagnosis, day of nephrology consultation, and day of initiation of renal replacement therapy). A striking feature of this cohort is the remarkable differences in patient characteristics, processes of care, and outcomes across clinical sites.[23] Table 2 demonstrates significant predictors of mortality using time-dependent covariates. The clinical and research applicability of this model needs to be tested in future studies.

Table 2 | Predictors of mortality using time-dependent covariates

Cox model (modified with permission from Chertow *et al.*[23])	Parameter	
	RR	95% CI
Age (per decade)	1.13	1.01–1.26
Sepsis[a]	1.87	1.33–2.63
CNS failure[a]	4.58	3.30–6.35
Liver failure[a]	1.90	1.34–2.71
Hematologic failure[a]	1.46	1.01–2.10
Dialysis[b]	1.79	1.21–2.66

CI, confidence interval; CNS, central nervous system; RR, relative risk.
[a]Sepsis status and organ system failure updated daily, last value carried forward where missing.
[b]Dialysis status carried forward after initiation.

Dysmetabolism in AKI

Critical illness leads to significant derangements in the metabolic milieu. Furthermore, the dysmetabolism accompanying critical illness is exacerbated in AKI by loss of kidney homeostatic function (Figure 3). These metabolic pathways represent potential therapeutic targets for improving outcomes. Severe illness of almost any etiology is accompanied by a generalized host inflammatory response, referred to as the systemic inflammatory response syndrome. Central to this process is the release of a cascade of potent inflammatory mediators into the systemic circulation, followed temporally by a compensatory anti-inflammatory response. The dysregulation of the inflammatory response in septic and critically ill patients has been implicated as an important mechanism underlying the development of multiple organ system dysfunction, septic shock, and death.[21] In critically ill

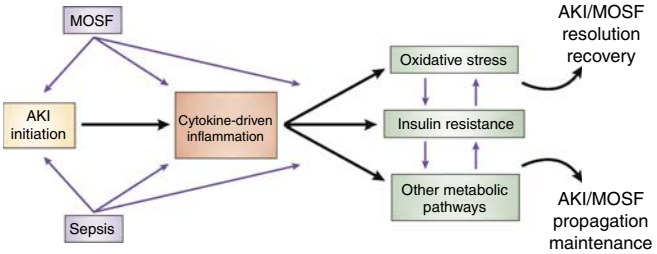

Figure 3 | A proposed mechanistic approach to dysmetabolism of AKI. The dysmetabolism of accompanying critical illness is exacerbated in AKI owing to loss of kidney homeostatic function. Once established, these metabolic derangements, along with other potential pathways including, but not limited to endothelial dysfunction, interact with each other to the extent that they may be the decisive factor leading to recovery or death. On the other hand, they also represent intriguing targets for future interventions in patients with AKI.

patients with AKI, pro- and anti-inflammatory cytokines are simultaneously markedly elevated, in the presence or absence of sepsis, and associated with significant and clinically meaningful increases in mortality risk.[24] Critically ill patients with AKI also have impaired monocyte cytokine production in a pattern that closely resembles other critically ill patients without AKI. These studies suggest that strategies designed to reduce inflammation in critically ill patients with established AKI should be attempted with caution so as not to exacerbate risk of infectious complications.

Hyperglycemia, along with other aspects of insulin resistance predict death and morbidity in the critically ill and are hallmarks of the so-called 'diabetes of injury.' Intensive insulin therapy designed to maintain blood glucose at or below 110 mg/dl can reduce morbidity and mortality in a surgical ICU and more recently in a medical ICU.[25,26] AKI patients may be even more likely to develop insulin resistance owing to additive effects of loss of kidney metabolic function, as the kidney plays an important role in glucose homeostasis. Consistent with these observations, critically ill patients with established AKI have significant insulin resistance, which is associated with mortality.[27] Whether or not hyperglycemia and/or hyperinsulinemia contribute directly to adverse events in critically ill patients with AKI or are simply a marker of metabolic injury severity has not been adequately established.

The dysregulated inflammatory response increases oxidative stress in patients with AKI. Furthermore, oxidative stress is an important pathogenic mechanism in the development of ischemic and toxic renal tubular injury. Kidney disease itself is now recognized as an additional stimulus for increased oxidative stress. Consistent with these observations, several recent studies indicate that critically ill patients with AKI manifest a marked increase in oxidative stress biomarkers.[28,29]

CONCLUSION

Nephrologists and intensivists are currently making a concerted effort to arrive at standardized terminology and classification of AKI. As a result, concepts concerning the lexicography, definitions, and epidemiolology of AKI are changing. Recent studies have dramatically advanced our understanding of the epidemiology and natural history of AKI, particularly in the hospital and ICU setting. Data indicate that small changes in kidney function have important prognostic implications, that the prevalence of AKI is increasing, and that associated mortality may be declining. Recent data also emphasizes that in critically ill patients with AKI, dysmetabolism (including dysregulated inflammation, insulin resistance, and increased oxidative stress) are exacerbated by the loss of kidney homeostatic function. Increasing knowledge concerning the natural history of AKI, particularly in the context of standardized definitions and classification, are critical for improved clinical decision-making, assessing processes of care, developing effective prognostication tools, and for the design of future clinical trials.

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